

# Doxycycline HCl (Vibramycin) as a single dose oral treatment of gonococcal and nonspecific urethritis in men

G. MASTERTON AND C. B. S. SCHOFIELD

Department of Venereology, 67 Black Street, Glasgow

Gonorrhoea is now said to be the second most common notifiable disease in the world, only measles being more prevalent. As stated in a recent leading article: 'With a mass measles vaccination just around the corner, it is a safe bet that gonorrhoea will take first place before very long' (*Lancet*, 1970). Nonspecific urethritis is even more common. In 1970 there were 36,996 cases of gonorrhoea in men and 16,556 in women in England, while in the same year there were 46,075 cases of nonspecific urethritis in men (Annual Report of the Chief Medical Officer, 1970).

Both gonococcal and nonspecific urethritis present problems in diagnosis and treatment, the most clamant possibly being in the latter category. A recent article (Phillips, Rimmer, Ridley, Lynn, and Warren, 1970) showed the relative resistance to penicillin, long the standard treatment in gonorrhoea, was found in 37 per cent. of gonococci isolated at St Thomas' Hospital in London, and although there is an evident variation in the sensitivity of strains in different parts of the country there is little doubt that this finding will become commonplace. Increasing the dose of penicillin is a self-limiting procedure, so there is need for an agent which will prove more effective against this common condition.

A further problem in the treatment of both gonococcal and nonspecific urethritis is that of administration of drugs and follow-up. It is a common experience to find that patients given a course of tablets may stop taking them as soon as the symptoms have been relieved, and there is little doubt that this practice has contributed to the persistence of partially resistant strains in the community. Patients fail to return to clinics for further treatment and investigation, so that the assessment of any new treatment for these conditions is rendered more difficult.

It was with these problems in mind that we undertook a trial of Vibramycin (doxycycline HCl) in the treatment of acute urethritis in male patients. This antibiotic had previously been shown to be effective in a single oral dose in the treatment of gonorrhoea

in men (Sylvestre and Gallai, 1968) and Domescik, McLone, Scotti, and Mackey, 1969). We have also assessed its effects in nonspecific urethritis.

## Method

241 consecutive male patients suffering from acute urethritis were admitted to the trial, and treated after diagnosis with a single dose of 300 mg. (3 capsules) of Vibramycin. No other treatment was given, and patients with complicated infections or those in transit were excluded from this survey.

## Diagnosis

Examination of Gram-stained urethral smears revealed gonococci in 107 cases, the relative sensitivity of each strain was determined to penicillin G, also the sensitivity or resistance to Vibramycin, tetracycline, streptomycin, kanamycin, and sulphafurazole. 107 strains were identified; 21 of these were resistant to streptomycin and eight to sulphafurazole. The range of sensitivities to penicillin G is shown in Table I.

TABLE I Initial sensitivities of the infecting gonococci

Minimum inhibitory concentration penicillin G ( $\mu$ g./ml.)	No. of cases	Resistance to	
		Streptomycin	Sulphafurazole
0.03	68	1	
0.06	19	3	
0.12	1	1	
0.15	13	11	4
0.3	4	3	2
0.6	1	1	1
1.2	1	1	1
Total	107	21	8

In the cases of the remaining 134 patients, examination of urethral smears and cultures excluded gonorrhoea, *T. vaginalis*, and *C. albicans*. These 134 patients were diagnosed as suffering from nonspecific urethritis.

## Results

Routine examinations were carried out on the 2nd, 4th or 5th, 8th, 15th, 22nd, and 29th days after treatment.

As always, in this type of survey, assessment was made difficult by the problem of the defaulting patient.

Five patients with gonorrhoea and twelve with nonspecific urethritis failed to return after treatment. A further 23 (21.4 per cent.) of those with gonorrhoea (Table II) and 37 (27.7 per cent.) of those with nonspecific urethritis (Table III) completed only one week's surveillance.

#### SIDE-EFFECTS

Nausea and vomiting were the only side-effects noted. Sixteen patients vomited and eight were nauseated out of 156 patients given Vibramycin capsules either alone or with Metoclopramide. We appreciate that the dosage of Metoclopramide was low (10 mg.) and it was administered only once. Of

the 85 other patients, who were given a glass of milk together with their dose of Vibramycin, only three were nauseated and none vomited. Reconstituted dried milk (non-fat and skimmed) was used successfully.

Treatment failed in four men in whom vomiting occurred within 30 minutes of medication. Two of the men had a gonococcal infection and the other two had nonspecific urethritis. Those patients who vomited later than this had apparently absorbed sufficient of the drug and were either cured or defaulted.

#### GONORRHOEA

Further antibiotic treatment was necessary in eight (7.5 per cent.) of the 107 patients because of the appearance of nonspecific urethritis (Table II).

TABLE II *Results — acute gonorrhoea*

Day	No. on surveillance	Last attendance	Subsequent default	Reason for withdrawal from trial		
				Subsequent antibiotics for other infections	Re-infection	Treatment failure
1	107	5	5			
2	102	18	16		1	1
4/5	84	12	3	4*		5
8	72	6	4	2*		
15	66	10	7	1*	2	
22	56	7	3	1*	3	
29	49	49				
Total		107	38	8*	6	6

\*Nonspecific urethritis

TABLE III *Results—nonspecific urethritis*

Day	No. on surveillance	Last attendance	Subsequent default	Reason for withdrawal from trial		
				Subsequent antibiotics for other infections	Re-infection	Treatment failure
1	134	12	12			
2	122	19	17	1 (A)		1
4/5	103	15	12	1 (B)		2
8	88	14	8	1 (C)	1 (D)	4
15	74	10	6		4 (E)	
22	64	4	2		1 (E)	1
29	60	60				
Total		134	57	3	6	8

A—*E. coli* cystitis  
B—*E. coli* cystitis

C— Intercurrent infection (multiple boils)  
D—Gonorrhoea

E—Nonspecific urethritis

Evidently, Vibramycin, which is effective in the treatment of that condition (see below), does not always exert a prophylactic action. These eight patients together with the five defaulters were excluded from the trial, leaving 94 who were followed.

Twelve patients had or developed gonococcal urethritis after treatment. As before, diagnosis was confirmed by culture. Of these patients, six (6.4 per cent.) were probably re-infected. This assessment was based on (1) admitted re-exposure to infection and (2) altered antibiogram of the infecting organism (Table IV).

In six (6.4 per cent.) the infection did not respond to Vibramycin, and, whether or not alcohol had been consumed, these were regarded as treatment failures.

The full period of surveillance was completed by 49 patients (45.8 per cent.), and they were clinically cured at that time.

#### NONSPECIFIC URETHRITIS

Fourteen of the 122 patients followed showed evidence of post-treatment urethritis during the period of surveillance (Table III).

Three patients requiring further antibiotic treat-

ment for other conditions (two had *E. coli* urinary infections and one developed furunculosis) were withdrawn from the survey.

Six admitted to further intercourse and were probably re-infected (five of these developed fresh nonspecific urethritis and one gonorrhoea). Eight of the remaining 119 cases (6.7 per cent.) failed to respond to treatment or developed complications during the period of surveillance, and must be regarded as treatment failures, although in two cases it is not possible to ascertain whether they were not complicated from the outset of treatment (Table V).

Sixty of the patients completed the full period of surveillance and were clinically cured at that time.

#### Discussion

The known failure rate in gonorrhoea in this series was 6.4 per cent. in the first four weeks after treatment. This is to be viewed in the light of the results we obtained in the same area using (a) 1 g. ampicillin intramuscularly and (b) 1 mega unit crystalline penicillin G (Table VI) Although the same standardized criteria are adopted in all our clinical trials, strict comparison is not valid.

TABLE IV *Gonococcal infection persisting after treatment*

Marital status	Age (yrs)	Promiscuous	Altered antibiogram	Re-exposure	Alcohol	Day of surveillance	Classification
W	55	Yes	Yes	Yes	Yes	21	Re-infection
S	25	Yes	No	Yes	No	21	
S	19	Yes	Yes	Yes	No	15	
Sep.	44	Yes	Yes	Yes	No	21	
S	17	Yes	Yes	Yes	Denied	18	
M	28	Yes	No	Yes	Yes	2	
M	23	No	No	Denied	No	5	Treatment failure
S	23	No	No	Denied	No	4	
M	24	No	No	Denied	Yes	4	
M	28	No	No	Denied	No	5	
S	24	Yes	No	Denied	No	2	
S	23	Yes	No	Denied	Yes	5	

TABLE V *Urethritis persisting after treatment (initial diagnosis nonspecific urethritis)*

Marital status	Age (yrs)	Promiscuous	Re-exposure	Alcohol	Additional diagnosis	Day of surveillance	Classification
M	38	Yes	Yes	Yes	Acute gonorrhoea	8	Re-infection
M	25	Yes	Yes	Yes	Nonspecific urethritis	15	
S	26	No	Yes	Yes	Nonspecific urethritis	15	
S	20	Yes	Yes	Yes	Nonspecific urethritis	15	
S	20	No	Yes	No	Nonspecific urethritis	15	
S	22	No	Yes	No	Nonspecific urethritis	22	
M	34	No	No	Yes		2	Treatment failure
M	26	No	No	No	Prostatitis	5	
S	22	No	No	No		5	
Div.	42	No	No	No		8	
S	18	No	No	Yes		8	
S	21	No	No	No	Prostatitis	8	
M	20	No	No	Yes		8	
S	50	No	No	No	Epididymitis	22	

The failure rate in NSU in this series was 6.7 per cent. Vibramycin failed to prevent the development of NSU in eight patients (7.5 per cent.) in whom it was effective in curing concurrent gonorrhoea. The results of treatment compare favourably with the failure rates observed using pyrrolidomethyl tetracycline 350 mg. intra-muscularly on 2 consecutive days (Schofield and Masterton, 1969), and the results using oral tetracycline given for either a 3- or 5-day course (Table VII).

Single dosage oral treatment for nonspecific urethritis is bound to be controversial, and we therefore deferred judgement until we could complete a long-term assessment at the end of a 12-month period of surveillance. It is well known that non-specific urethritis, when treated with the tetra-

cycline group, has a disappointingly high recurrence rate. In fact, fewer cases of long-term recurrences presented after single dosage Vibramycin treatment than after other more prolonged tetracycline regimes (Table VIII). For purposes of comparison, we made no attempt to differentiate between re-infection and relapse and nearly half of these recurrent infections appeared within the first 2 months of surveillance (Table IX).

The great advantage of Vibramycin is its effectiveness against both gonorrhoea and NSU in a single oral dose. Immediate oral treatment is clearly of value in those isolated centres which can be medically supervised only occasionally. Since Vibramycin is equally effective against both NSU and gonorrhoea, immediate diagnosis is no longer so essential. For

TABLE VI *Comparison of results in treatment of acute gonorrhoea*

Year	Drug	Dosage	No. of patients	Percentage known failure rate
1968	Crystalline penicillin	1 mega unit intramuscularly	280	10.4
1969	Ampicillin	1 g. intramuscularly	194	5.8
1969-70	Vibramycin	300 mg. (oral)	107	6.4

TABLE VII *Comparison of results in treatment of nonspecific urethritis*

Year	Drug	Mode of administration	Dosage (mg.)	Length of course (days)	No. of patients	Percentage known failure rate
1969	Oxytetracycline	Oral	250 4 times a day	3	150	13.3
1969	Oxytetracycline	Oral	250 4 times a day	5	100	12.0
1969	Oxytetracycline	Oral	500 4 times a day	4	120	11.4
1969	Pyrrolidomethyl Tetracycline	Intramuscular injection	350	2	96	6.4
1969-70	Vibramycin	Oral	300	One only	119	6.7

TABLE VIII *12 months' post-treatment surveillance*

Drug	Dosage (mg.)	Length of course (days)	No. of patients treated	Total no. of recurrences	No. of patients with recurrence	Percentage of patients initially treated
Oxytetracycline	250 4 times a day	3	134	34	23	17.1
Oxytetracycline	250 4 times a day	5	134	28	18	13.4
Vibramycin	300	One only	134	22	15	11.2

TABLE IX *Time interval before recurrence of urethritis*

Drug	Interval between clearance and recurrence of symptoms (mths)								Total recurrences
	1	2	3	4	5	6	7	8-12	
3-day oxytetracycline	11	9	5	5	1	1	2	0	34
5-day oxytetracycline	5	10	7	1	1	2	2	0	28
Vibramycin	3	8	8	2	1	-	-	0	22

epidemiological and social reasons, of course, it remains imperative that a proper diagnosis, including cultural investigations, should be made as soon as possible, but in situations in which a microscope is not available, it would be possible to give a single dose of 300 mg. Vibramycin to all men with uncomplicated urethritis (the appropriate tests having been previously taken, such as smears and charcoal swabs in Stuart's transport medium) with a good chance of cure whether the ultimate diagnosis was gonorrhoea or nonspecific urethritis.

Vibramycin is the obvious choice for the 'needle-shy' patient, and it should be of value on merchant vessels when urethritis is treated in the absence of a doctor, slides having been previously taken in accordance with the 'Ship Captain's Medical Guide' (1967). The incidence of side-effects is low: in this series the few cases of nausea and vomiting were easily controlled by the administration of a glass of milk together with the single dose of Vibramycin.

Current practice in dealing with strains of *N. gonorrhoeae* increasingly resistant to penicillin is to increase the dose of penicillin, but this is a self-limiting procedure. Alternative antibiotic treatment is also being given, and Vibramycin has been shown in this series to be an effective agent in the treatment of both gonorrhoea and nonspecific urethritis, penicillin being ineffective against the latter.

The main advantages of Vibramycin in this field are therefore its overall effectiveness against both gonorrhoea and nonspecific urethritis, and the fact that a treatment curative for the majority of cases can be administered as a single oral dose in the presence of the clinician or nurse, thus ensuring that the whole of the treatment is effectively taken without having recourse to injection.

### Summary

107 male patients suffering from acute gonococcal urethritis and 134 male patients suffering from non-specific urethritis, were treated with a single oral dose of 300 mg. Vibramycin. Our low failure rate was 6.4 per cent. in 94 cases of uncomplicated gonorrhoea which were followed, and 6.7 per cent. in 119 cases of nonspecific urethritis. These results compare well with those obtained at the same clinics using crystalline penicillin or ampicillin in gonococcal infections and oxytetracycline in nonspecific urethritis. Nausea and vomiting were easily prevented by the concurrent administration of 50 ml. reconstituted dried fat-free milk.

Vibramycin failed to prevent the development of nonspecific urethritis when administered to patients who had contracted both this and gonorrhoea at the same time. Its high degree of therapeutic effective-

ness and the simplicity of dosage, as well as the fact that in isolated centres it allows immediate effective treatment of either type of urethritis to be carried out in advance of bacteriological confirmation, makes Vibramycin an agent of choice in the treatment of both acute gonorrhoea and nonspecific urethritis.

We wish to thank Dr T. F. Elias-Jones, Director of the City Laboratory, Glasgow, who was responsible for the bacteriological aspects of this work, and also Dr F. J. A. Bateman, Medical Director of Pfizer Limited, who supplied the Vibramycin used and for his valuable assistance in the preparation of this paper.

### References

- 'Annual Report of the Chief Medical Officer for 1970' (1971) H.M.S.O., London
- DOMESCIK, G., McLONE, D. G., SCOTTI, A., and MACKEY, D. M. (1969) *Publ. Hlth Rep. (Wash.)*, **84**, 182
- Lancet* (1970) **1**, 280
- PHILLIPS, I., RIMMER, D., RIDLEY, M., LYNN, R., and WARREN, C. (1970) *Lancet*, **1**, 263
- SCHOFIELD, C. B. S., and MASTERTON, G. (1969) *Brit. J. vener. Dis.*, **45**, 47
- 'Ship Captain's Medical Guide' (1967) pp. 300 et seq. H.M.S.O., London
- SYLVESTRE, L., and GALLAI, Z. (1968) *Un. méd. Canad.*, **97**, 639

### La Vibramycine (doxycycline HCl) employée en traitement oral en une seule dose dans les urétrites gonococciques et non gonococciques masculines

#### SOMMAIRE

107 malades atteints d'urétrite gonococcique aigüe et 134 hommes atteints d'urétrite non gonococcique furent traités par une dose buccale unique de 300 mg. de Vibramycine. Notre bas taux d'échec fut de 6,4% pour les 94 cas de gonococcie non compliquée qui ont été suivis et de 6,7% pour les 119 cas d'urétrite non gonococcique. Ces résultats se comparent bien avec ceux obtenus dans les mêmes cliniques avec la pénicilline cristalline ou l'ampicilline dans les infections gonococciques, ou avec l'oxytétracycline dans les urétrites non gonococciques. L'administration simultanée de 50 ml. de lait sec exempt de graisse, reconstitué, empêcha facilement les nausées et les vomissements.

La Vibramycine ne réussit pas à prévenir l'apparition d'urétrite non gonococcique lorsqu'elle fut prescrite à des malades ayant contracté en même temps cette urétrite et la gonococcie. Son haut niveau d'efficacité thérapeutique et la simplicité de la posologie, ainsi que le fait que, dans les centres isolés, un traitement efficace et immédiat peut être appliqué dans les deux types d'urétrite avant la confirmation bactériologique, fait de la Vibramycine un médicament de choix aussi bien dans la gonococcie aigüe que dans l'urétrite gonococcique.